## REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1 to 10 and 12 to 49, the only claims pending and under examination in this application.

Claims 13 and 37 has been amended to clarify the language by removing the term "finally." In addition, claim 20 has been amended to specify that the composition includes an absorption complex of a chitosan componant and an agent, support for this amendment being found in the specification at page 6, lines 24-27. As the above amendments introduce no new matter, their entry by the Examiner is respectfully requested.

Claims 13-26 and 37-49 have been rejected under 35 U.S.C. § 112, second paragraph, for use of the term "finally." In view of the above amendments to claims 14 and 37, this rejection may be withdrawn.

The Examiner has next rejected original claims 20 and 22, as well as claims 21, 23, 24, 25 and 26 as being unpatentable 35 U.S.C. § 103(a) over Roser I (US 5,149,653) in view of Illum et al (US 6,391,318) and Chatfield (US 6,136,606) and in view of Roser PCT (WO 96/40077) and Roser II (US 6,221,575). The Examiner has maintained this rejection for the asserted reason that the novel element of the methods claims of first forming a coacerative between the biological material and chitosan does not appear as a recited structural element in the composition of matter claims. Following entry of the above amendments, claim 20, and dependent claims 21 to 26 by virtue of their dependency thereon, all require the composition to include an absorption complex of the biologically active material and the chitoson component. None of the cited references, either alone or in combination, teach or suggest such an element in a composition, as they fail to teach or suggestion method that first produces a coacerative of chitosan and biologically active agent. Accordingly, this rejection may be withdrawn.

Next, claims 1-3, 5-10, 12-14, 16-25, 27-29, 31, 33-39, 41-43 and 45-49 have been rejected as obvious under 35 U.S.C. § 103(a) over Roser I (US 5,149,653) in view of Illum et al (US 6,391,318) and Chatfield (US 6,136,606) and in view of Roser PCT (WO 96/40077) and Roser II (US 6,221,575), and further in view of Herbert and Orly.

As explained previously, the present invention is a method of preserving biologically-active material, as well as compositions produced by the method. The claimed method comprises a first step wherein an aqueous suspension of the biologically-active material is mixed with an aqueous solution of chitosan (or non-toxic salt thereof) so as to form a coacervate. The coacervate, as explained in the specification at page 6, lines 24-27, is an absorption complex of the chitosan and the biologically-active material wherein the biologically-active material is coated with the chitosan to form a protective "shell" around the biologically-active material (specification, page 6, lines 6-8). Following the formation of the coacervate, it is then mixed with the trehalose solution. The mixture obtained is then subjected to drying at a pressure less than atmospheric and at a temperature which is initially less than or equal to 37°C and which temperature is prevented from falling to 0°C or below to form a glassy trehalose matrix containing, within the matrix, desiccated biologically-active material and chitosan (or non-toxic salt thereof).

As acknowledged by the Examiner in the present office action, the combined teaching of Roser I (US 5,149,653) in view of Illum et al (US 6,391,318) and Chatfield (US 6,136,606) and in view of Roser PCT (WO 96/40077) and Roser II (US 6,221,575) fails to teach or suggest a method that includes a first step of making an agent/chitosan component coacervate and then, in a second step, vacuum drying the resultant coacervate.

To make up for this acknowledged deficiency, the Examiner looks to the teachings fo Hebert and Orly. The Examiner says (official action, page 5, starting six lines from the bottom of the page) that the teachings of Herbert and Gander (presumably 'Orly et al' is intended) indicate that one method for making microparticles comprising a bioactive agent is through making a coacervation of the agent and the polymer used to form the particle. The Examiner therefore concludes that: "Thus, it would have been obvious to those in the art attempting to preserve a vaccine through freeze-drying to add trehalose to a microparticle coacervate and to perform the drying described by the Roser references".

The Herbert et al reference is concerned with the preparation of biodegradable microparticle comprising a biodegradable polymeric binder and a biologically-active agent. According to Herbert et al, column 7, lines 55 to 63, the invention disclosed therein involves

the use of a solvent blend, free from halogenated hydrocarbons, comprising at least two solvents to produce biodegradable microparticles comprising at least one biologically-active agent. A first solvent component of the solvent blend is a poor solvent for the active agent but is a good solvent for the biodegradable polymer. A second solvent component of the solvent blend is a good solvent for both the active agent and the polymer. According to column 8, lines 28 to 39, the solvent system is a blend of at least two solvents which are:

(1) mutually miscible with one another ;
(2) capable, when blended, of dissolving or dispersing the active agent;
(3) capable, when blended, of dissolving polymeric matrix material; and
(4) substantially immiscible with the quench liquid.

It will be appreciated, therefore, that the invention taught by Herbert et al involves the preparation of biodegradable microparticles by using a special blend of solvents.

In Herbert et al, the biodegradable microparticles are intended as a means for delivering drugs or other biologically-active agents to the body in a controlled or sustained release (column 7, line 65 to column 8, line 19). The biodegradable polymer is one that is biodegradable in the body so as to permit all of the entrapped agent to be released in the body of the patient (column 8, lines 14 to 19). There is no teaching or suggestion in Herbert et al that the biodegradable polymer affords any protection to the biologically-active agent in any method of dehydrating that agent. The list of examples of biodegradable polymers given in Herbert et al (column 9, line 50 to column 10, line 13) does not mention chitosan or non-toxic salts of chitosan.

Thus, the disclosure in Herbert et al does not provide any motivation to a skilled person to use chitosan to enhance thermal tolerance of a thermally-sensitive biologically-active agent in a method of preserving that thermally sensitive biologically-active agent by desiccation and gives no reason to a person skilled in the art why chitosan should be employed in the way that it is employed in the present invention.

Orly et al also (like Herbert et al) discloses a method for producing microparticles. The method disclosed by Orly et al (according to column 2, lines 5 to 21) is characterized in

that an essentially homogeneous solution of a substance or mixtures of substances in a solvent is first prepared, an emulsion of the solution is produced in a dispersing liquid forming a continuous phase, in which said substance or said mixture is essentially insoluble, and forming a disperse phase, and a chemical or physicochemical reaction is then initiated in the disperse phase by modification of the in-situ chemical composition of said substance or said mixture in the disperse phase through the addition of an agent which is essentially insoluble in or immiscible with the continuous phase, under the conditions of addition, thereby modifying the physicochemical state and resulting in the insolubilization of the substance or mixture of substances and the individualization of the microparticles. As such, Orly discloses a method that uses the interaction of different solvents to ensure that very small particles of a substance, such as chitosan (column 2, line 57 and column 5, lines 39 to 55) are created. Such microparticles may be used to deliver drugs. The object of the invention of Orly et al is to manufacture microparticles, in particular microcapsules, by a simple and inexpensive process which makes it possible to adjust the size of the particles obtained whilst avoiding the need to use difunctional crosslinking agents which would jeopardise the biocompatibility of the microparticles. Like Herbert et al, Orly et al is concerned solely with producing microparticles (which in the case of Orly et al may be formed of chitosan).

There is no suggestion in Orly et al that chitosan (or a non-toxic salt) enhances the thermal tolerance of a thermally sensitive biologically-active agent subjected to desiccation by vacuum dehydration in a trehalose solution. Thus, there is no motivation for a person skilled in the art to form a coacervate of chitosan and a biologically-active agent using aqueous based media prior to subjecting the coacervate to dehydration in a trehalose solution.

The rejection is based on the assumption that because Orly or Herbert teach the production of biopolymeric microparticles, which in the case of Orly may be fabricated from chitoson, one of skill in the art would be motivated to take these microparticles and vacuum dry them and therefore arrive at the subject methods and compositions.

However, the microparticles produced in Herbert and in Orly are prepared to have particular properties. The skilled person would not, after following the involved Herbert and

Orly procedures, submit the products to vacuum dehydration with the risk that the particular properties achieved might be compromised, unless there was a clear motivation to do this. No motivation exists since none of the prior art references suggest that the use of chitosan would enhance the thermal tolerance of a thermally sensitive biologically-active material during desiccation.

Furthermore, in both Herbert et al and Orly et al, the procedure for making a microparticle is complex and involves the use of different solvents (not just mixing aqueous suspension/solutions). Thus, even the method of making the coacervate in the present invention is not the same as the methods employed in Herbert and Orly. In addition, if a person skilled in the art did add trehalose to a microparticle coacervate prepared according to Herbert or to Orly, the method would be different from that claimed in claim, as the recited protocol of such a combined methodology would still not teach or suggest the claimed methods and compositions.

For the reasons provided above, claims 1-3, 5-10, 12-14, 16-25, 27-29, 31, 33-39, 41-43 and 45-49 are not obvious under 35 U.S.C. § 103(a) over Roser I (US 5,149,653) in view of Illum et al (US 6,391,318) and Chatfield (US 6,136,606) and in view of Roser PCT (WO 96/40077) and Roser II (US 6,221,575), and further in view of Herbert and Orly, and this rejection may be withdrawn.

Next, Claim 4 has been rejected under 35 U.S.C. § 103(a) as obvious over Roser I (US 5,149,653) in view of Illum et al (US 6,391,318) and Chatfield (US 6,136,606) and in view of Roser PCT (WO 96/40077) and Roser II (US 6,221,575) and further in view of Herbert and Orly; and further in view of Rweyemamu et al and Gombotz et al (US 5,900,238). In view of the fundamental deficiency in the primary seven references as discussed above, and the fact the final two references cannot make up this fundamental deficiency, this rejection may be withdrawn.

Finally, Claims 1, 2, 5, 7-10, 12-14, 16-24, 27, 28, 31, 33-38, 41-43 and 45-48 have been rejected under 35 U.S.C. § 103(a) as obvious over Roser I (US 5,149,653) in view of Illum et al (US 6,391,318) and Chatfield (US 6,136,606) and in view of Roser PCT (WO 96/40077) and Roser II (US 6,221,575) and further in view of Roy et al (US 5,972,707).

Roy et al teaches a composition comprising solid nanospheres for gene delivery to cells comprising a polymeric cation, which can be chitosan, and nucleic acids. According to the Examiner, once the coacervate of the chitosan and nucleic acid described in Roy et al had been made, it would have been obvious to those skilled in the art to use methods disclosed in the Roser references to preserve the material until ready for use.

However, Roy merely teaches that a chitosan delivery system for the nucleic acids can be made by a simple method of coacervation. The teaching in Roy et al is that the use of chitosan has the advantage of permitting the direct use of freshly made coacervates to transfect cells (column 7, lines 36-40). Thus, it would seem unlikely that a person skilled in the art would make such coacervates and then preserve them in the way suggested by the Examiner (it would be more likely that the nucleic acid material would, if necessary, be preserved according to Roser and then, when it is desired to use the invention of Roy et al, would be recovered and then combined with the chitosan according to Roy et al for immediate use). The Examiner has not suggested that there is any reason why the skilled person would be motivated to create the nanoparticulate chitosan-nucleic acid product according to Roy et al and then preserve it according to Roser.

As discussed above, the present invention is a method of preserving a biologically-active material and is based on the discovery that the formation of a coacervate between chitosan and the biologically-active material enhances the thermal tolerance of the biologically-active material whilst being subjected to desiccation during vacuum dehydration of a trehalose solution containing it. There is no suggestion in Roy et al of this technical effect.

Roy et al mentions (column 7, lines 33-34) that chitosan based nanospheres can be freeze dried and are storage stable. If this statement is actually referring to the chitosan-coacervate then it has to be said that if these coacervates can be freeze dried then there would be no motivation for a skilled person to submit such coacervates to vacuum drying in a trehalose solution according to Roser. Since the controlled dehydration conditions of the present invention are necessary for thermosensitive materials which would lose their potency in a conventional freeze drying procedure (see the introduction in the present

specification), there seems to be no reason why a skilled person would be motivated to subject chitosan-nucleic acid coacervates to such a procedure if they can simply be freeze dried.

As such, one of skill in the art would not be motivated to subject the nanoparticles produced by Roy to the vacuum drying second step of the presently claimed methods.

Accordingly, Claims 1, 2, 5, 7-10, 12-14, 16-24, 27, 28, 31, 33-38, 41-43 and 45-48 are not obvious under 35 U.S.C. § 103(a) in view of Roser I (US 5,149,653) in view of Illum et al (US 6,391,318) and Chatfield (US 6,136,606) and in view of Roser PCT (WO 96/40077) and Roser II (US 6,221,575) and further in view of Roy et al (US 5,972,707) and this rejection may be withdrawn.

## CONCLUSION

In view of the above amendments and remarks, this application is condidered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STHP-002.

Respectfully submitted,
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